UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,286	12/13/2001	David Flyer	26747-34	2366

7590 07/12/2005

CARELLA, BYRNE, BAIN, GILFILLAN, CECCHI,
STEWART & OLSTEIN
6 Becker Farm Road
Roseland, NJ 07068

EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/022,286	FLYER ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-42* is/are pending in the application.

4a) Of the above claim(s) *5-13,15-23,26-29,31 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,24,25,30 and 33-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

3.00

DETAILED ACTION

1. Applicant's response filed 4/29/05 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group I (claims 1-8, 14 and 24-30), and species of SEQ ID NO: 1.

Claims 5-8 and 26-29 (non-elected species of Group I) and claims 9-13, 15-23 and 31-32 (non-elected groups II-VIII) remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Applicant is reminded that upon consideration of the prior art, the search had been extended to include SEQ ID NO: 5.

Claims 1-4, 24, 25, 30 and 33-42 are currently being examined as they read upon SEQ ID NO: 1 and SEQ ID NO: 5.

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP 602.01 and 602.02.

The oath or declaration is defective because: although another declaration has been submitted and signed by inventor Flyer, the other inventors have not signed and dated the declaration.

The following are new grounds of rejection necessitated by Applicant's amendment filed 4/29/05.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 24, 25, 30 and 33-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification

does not convey to the artisan that the Applicant had possession at the time of invention of the claimed immunogen, pharmaceutical composition and vaccine thereof, recited in the instant claims.

The instant claims encompass (1) an immunogen or molecule that induces a CTL-response, said immunogen or molecule comprising one or more peptides each containing the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 5 or a sequence differing from said sequence by not more than one amino acid residue from the sequence of SEQ ID NO: 1 or SEQ ID NO: 5, and wherein said immunogen is not hsp65 protein, and composition thereof, or (2) an isolated peptide comprising the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 5 or a sequence differing by no more than one amino acid residue from the sequence of SEQ ID NO: 1 or SEQ ID NO: 5 and composition thereof; (3) a molecule that induces a CTL response, said molecule comprising a plurality of peptides each containing the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 5 or a sequence differing from said sequence by not more than 1 amino acid residue and wherein said molecule is not hsp65 protein, including wherein at least one said peptide comprises SEQ ID NO: 1 and at least one said peptide comprises the amino acid sequence of SEQ ID NO: 5. There is insufficient disclosure in the specification on such an immunogen/molecule/peptide and composition thereof.

As such, the instant claims encompass a polypeptide sequence/composition thereof that induces a CTL response to any subsequence of the polypeptide that is restricted by any MHC class I molecule, and wherein the polypeptide comprises a copy or copies of one of SEQ ID NO: 1 and/or SEQ ID NO: 5 or 1 amino acid residue substitution/deletion or addition variants thereof present in the said polypeptide with undisclosed flanking sequences.

The specification discloses that the sequence of SEQ ID NO: 5 is found in M. *bovis* HSP65, that the peptides of SEQ ID NO: 2, 3 and 4 are derived from an M. *tuberculosis* hypothetical protein "Rv0341", that the peptide SEQ ID NO: 1 is derived from an M. *tuberculosis* hypothetical protein "Rv3808c", and the said SEQ ID NO have been found in association with HLA-A2 in mammalian cell lines infected with M. tuberculosis and are useful as an immunotherapeutic in the prevention and treatment of tuberculosis (page 14 at lines 17-21 and page 20 at lines 9-16). The specification further discloses that the peptides can be used for the prevention, treatment and diagnosis of bacterial infections, especially tuberculosis (page 14 at lines 10-12). The specification discloses that the polypeptides can be of any desired length so long as they have immunogenic activity in that they are able, to elicit in vitro or in vivo the activation of CTL against a presentation of TB-infected cells when such polypeptides are presented along with MHC class I proteins (page 16 at lines 10-18). The specification discloses that the immunogenic peptides may be part of an immunogenic structure via attachments other than conventional peptide bonds (paragraph spanning pages 21 and 22). The specification discloses that peptides can be modified at positions that bind MHC class I or at positions that interact with TCR on CTL (page 22 at lines 7-22). The specification

discloses that the peptides may have up to 2 substitutions, so long as they have substantially identical antigenic activity (pages 24 at lines 25-28).

The specification does not disclose any immunogen *comprising* SEQ ID NO: 1 or 5 or one *comprising* the SEQ ID NO differing by not more than one amino acid residue used as an immunogen. The specification does not disclose that SEQ ID NO: 1 or 5 are immunogenic with respect to induction of CTL, just that they are expressed on infected cells bound to HLA-A2.1. The specification does not disclose any peptides or immunogens comprising SEQ ID NO: 1 or 5 that have flanking amino acid residues, nor does the specification disclose any other restriction element for the SEQ ID NO except for HLA-A2.1.

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera, including peptides that are variants within the said SEQ ID NO or that have flanking sequence of undisclosed identity and any length that does not necessarily include sequences flanking the said SEQ ID NO in the protein of origin. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

Applicant's arguments in Applicant's amendment filed 4/29/05 have been fully considered, but are not persuasive.

Applicant's arguments are of record in the said amendment, briefly: (1) that Applicant has amended claim 1 to recite a molecule that induces a CTL response and that comprises one or more copies of the recited peptides; (2) that Applicant has provided both structural and functional features of such a molecule since SEQ ID NO: 1 or 5 have only one addition, deletion or substitution and that the molecule elicits a CTL response, respectively; (3) that the assay for stimulation of a CTL response is disclosed and requires no undue experimentation.

It is the Examiner's position: (1) that the instant claims encompass one or more copies of a peptide that *comprises* one of SEQ ID NO: 1 or 5 or a one amino acid residue deletion, addition or substitution variant thereof, *i.e.*, has undisclosed flanking sequence; (2) that although SEQ ID NO: 1 or 5 are fully defined 9-mer sequences, the claims encompass a polypeptide that comprises one or more peptides *comprising* SEQ ID NO: 1 and/or 5 or the said variant thereof that can elicit a CTL response *to any MHC class I restriction element, not necessarily HLA-A2.1*; (3) that in light of this, the assay for stimulation of a CTL response is in the context of CTL restricted by any peptide that is comprised in the said polypeptide that binds to any class I MHC restriction element, said peptide including neoepitopes and peptides that are unrelated to SEQ ID NO: 1 and/or 5.

6. Claims 1-4, 24, 2, 30 and 33-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and use the instant invention: (1) an immunogen or molecule that induces a CTL-response, said immunogen or molecule comprising one or more peptides each containing the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 5 or a sequence differing from said sequence by not more than one amino acid residue from the sequence of SEQ ID NO: 1 or SEQ ID NO: 5, and wherein said immunogen is not hsp65 protein, and composition thereof, or (2) an isolated peptide comprising the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 5 or a sequence differing by no more than one amino acid residue from the sequence of SEQ ID NO: 1 or SEQ ID NO: 5 and composition thereof; (3) a molecule that induces a CTL response, said molecule comprising a plurality of peptides each containing the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 5 or a sequence differing from said sequence by not more than 1 amino acid residue and wherein said molecule is not hsp65 protein, including wherein at least one said peptide comprises SEQ ID NO: 1 and at least one said peptide comprises the amino acid sequence of SEQ ID NO: 5. The specification has not enabled the breadth of the claimed invention because the instant claims encompass a polypeptide sequence/composition that induces a CTL response to any subsequence of the polypeptide, not necessarily SEQ ID NO: 1 and/or 5 that is restricted by any MHC class I molecule, and wherein the polypeptide comprises a copy or copies of one of SEQ ID NO: 1 and/or SEQ ID NO: 5 or 1 amino acid residue substitution/deletion or addition variants thereof present in the said polypeptide with undisclosed flanking sequences. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed immunogens/molecules/peptides/ compositions can be made and/or used. The specification discloses no working examples with regards to the use of the instant peptides of SEQ ID NO: 1-5 for immunization, prevention or treatment *in vitro* or *in vivo*.

The specification discloses that the sequence of SEQ ID NO: 5 is found in M. *bovis* HSP65, that the peptides of SEQ ID NO: 2, 3 and 4 are derived from an M. *tuberculosis* hypothetical protein "Rv0341", that the peptide SEQ ID NO: 1 is derived from an M. tuberculosis hypothetical protein "Rv3808c", and the said SEQ ID NO have been found in association with HLA-A2 in mammalian cell lines infected with M. *tuberculosis* and are useful as an immunotherapeutic in the prevention and treatment of tuberculosis (page 14 at lines 17-21 and page 20 at lines 9-16). The specification further discloses that the peptides can be used for the prevention, treatment and diagnosis of bacterial infections, especially tuberculosis (page 14 at lines 10-12). The specification discloses that the polypeptides can be of any desired length so long as they have immunogenic activity in that they are able, to elicit in vitro or in vivo the activation of CTL against a presentation of TB-infected cells when such polypeptides are presented along with MHC class I proteins (page 16 at lines 10-18). The specification discloses that the

immunogenic peptides may be part of an immunogenic structure via attachments other than conventional peptide bonds (paragraph spanning pages 21 and 22).
The specification discloses that peptides can be modified at positions that bind MHC class I or at positions that interact with TCR on CTL (page 22 at lines 7-22). The specification discloses that the peptides may have up to 2 substitutions, so long as they have substantially identical antigenic activity (pages 24 at lines 25-28).

The specification does not disclose any immunogen *comprising* SEQ ID NO: 1 or 5 or one *comprising* the SEQ ID NO differing by not more than one amino acid residue used as an immunogen. The specification does not disclose any peptides or immunogens comprising SEQ ID NO: 1, or 5 that have flanking amino acid residues. The specification does not disclose that SEQ ID NO: 1 and/or 5 are immunogenic with respect to induction of CTL response, just that the said SEQ ID NO are present on the surface of infected cells bound to HLA-A2.1.

Evidentiary reference Vordermeier et al (Scand. J. Immunol. 45, 521-526, 1997, IDS reference) teach epitopes from hsp65 and 38KDa lipoglycoprotein antigens of M. *tuberculosis*, and that it appears that production of large amounts of γ-IFN by the responding CTL line is of critical importance in protective anti-tuberculous immune responses. Vordermeier et al teach that peptide vaccination does not reflect a physiological way of CTL induction similar to that by infection or following vaccination with tubercle bacilli, and the instant specification does not disclose any therapeutic or prophylactic result using the said SEQ ID NO or peptides comprising the said SEQ ID NO with substitutions or flanking sequences.

As to the issue of "*comprising*", the specification does not disclose wherein the peptides constitute a CTL epitope and additional sequences that are not a T cell epitope. It is unpredictable that said peptide would bind to MHC class I and would be recognized by CTL, i.e., be a T cell epitope. The MHC class I restriction element is not recited in the instant claims, nor is it recited that the peptide *consisting of* the SEQ ID NO elicits a CTL response, but rather than the immunogen *comprising* the peptide *comprising* the SEQ ID NO induces a CTL response. The specification provides no evidence that the peptide comprising the said SEQ ID NO: (1) would bind to any MHC molecule, in particular to HLA-A2, when present in a longer peptide of unknown length and flanked by amino acid sequences not present in the antigenic protein of origin, (2) or would be recognized by CTL. In addition, the art recognizes that flanking sequences influence the processing and presentation of CTL epitopes (Eisenlohr et al, Shastri et al, Bergmann et al, Wang et al, Perkins et al, Theobald et al and Gileadi et al), that immunodominance can be affected by the context of the epitope within the protein molecule and that junctional neoepitopes can be created (Perkins et al) or that immunodominant epitopes can be completely silenced by contiguous sequences (Wang et al). An undue amount of experimentation would be involved in determining longer peptides from the many possibilities that would be capable of binding to HLA and being

recognized by CTL. In addition, Anderton et al teaches that *in vivo* use of altered peptide ligands is unpredictable and dangerous in outbred human populations.

In addition, the art recognizes that for a peptide to be a T cell epitope, the length of the peptide is important for binding to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The claims do not recite a length limitation for the peptide sequence that binds the MHC class I molecule and induces a CTL response. The peptides that bind to class I molecules have a predominant length, i.e., a minimum of 8 or 9 amino acid residues for a class I MHC restricted T cell epitope peptide. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets ("A","F") located at opposite ends of the binding groove of the class I molecule, giving rise to a common orientation of the peptides in the binding site (Engelhard at page 14, column 1, lines 16-27.) Thus, the amino acid residues at the peptides' termini make a network of hydrogen bonds with conserved residues on the sides and bottom of the peptide binding groove of class I molecules. These interactions are important for holding the peptides in the binding groove and for stabilizing the complex (Guo, et al at page 366, column 1 lines 1-10.) "...the preferred length (of the peptide) is determined by the minimum amount of peptide required to span the center of the binding site and optimize the interactions at the ends" , but that the predominant length is 9 amino acid residues (Engelhard at page 14, column 1, lines 23-27). The minimum length for a peptide to be a T cell epitope for class I MHC is 8-9 amino acid residues (Rammensee et al at page 182, column 2, last paragraph).

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

Applicant's arguments in Applicant's amendment filed 4/29/05 have been fully considered, but are not persuasive.

Applicant's arguments are of record in the said amendment, briefly: (1) that the invention relates to MHC class I epitopes of a given structure and length because early TB infection is an MHC class I [mediated] process and not MHC class II like other microbial infections; (2) that the assay for stimulation of a CTL response is disclosed, and using it does not constitute undue experimentation; (3) that a use is described in the application at page 33 at line 18 to page 34 through line 17 and Example 4 on page 45; (4) that the specification discloses proteins in which some of the peptides were found and that these, except for Hsp65 may be immunogenic, including *in vitro*; (5) that the claims are composition of matter claims not method claims; (6) that SEQ ID NO: 5 was disclosed in the instant specification to be produced and expressed by an antigen presenting cell; (7) that that since Applicant has provided defined SEQ ID NO, assays to be run to determine a proper CTL inducing sequence when the said SEQ ID NO are flanked by undisclosed sequence does not rise to the level of undue experimentation;

(8) that the Examiner cites Mohaghenghpour *et al* for the teaching of importance of CTL in protective immunity against M. *tuberculosis*.

It is the Examiner's position that: (1) the claims are not drawn to a peptide of given structure and length, but rather to a polypeptide or molecule *comprising* a peptide(s) that *comprises* a SEQ ID NO that is defined or that differs by one amino acid residue from the said SEQ ID NO and the SEQ ID NO or some other subsequence in the polypeptide capable of binding to an MHC class I molecule is a given structure and length; (2) and (7) since the claims are not drawn to a peptide of limited length that induces a CTL response but rather to a polypeptide immunogen or molecule *comprising* a peptide(s) that *comprises* a SEQ ID NO that is defined or that differs by one amino acid residue from the said SEQ ID NO, and the claims recite that the polypeptide immunogen or molecule induces a CTL response not that the SEQ ID NO induces the CTL response and MHC class I restriction element is not recited in the claims, the portion of the polypeptide immunogen that elicits the CTL response need not be one of SEQ ID NO: 1 or 5. Thus, making and testing such a polypeptide immunogen, said immunogen comprising undisclosed flanking sequence surrounding one or a number of peptides comprising one of SEQ ID NO: 1 or 5 does constitute undue experimentation, said testing being for processing of the immunogen, binding to any class I MHC molecule and eliciting the corresponding restricted CTL response; (3), (4) and (6) the claims under instant rejection recite not only SEQ ID NO: 5 but also SEQ ID NO: 1. The disclosed use of the immunogen at the said locations in the specification cited by Applicant is to screen a sample for the presence of CTLs that specifically recognize the corresponding epitopes (pages 33-34) and that the SEQ ID NO: 1 and 5 were expressed on the surface of a malignantly transformed macrophage U937/HLA-A2.1 positive cell line infected with an avirulent strain of M. *tuberculosis* (Example 4 on page 45). It is the Examiner's position that this disclosure shows that the peptides are processed by the said cell line but not that CTL can be generated in response to the peptides, and does not demonstrate that CTL precursors specific for the peptides are present in uninfected or virulent strain infected individuals. In addition, the specification discloses that SEQ ID NO: 1 is from a hypothetical protein encoded by an open reading frame within the M. *tuberculosis* genome, but there is no disclosure of any physiological relevance of a CTL response to said hypothetical protein or that one can indeed by elicited; (8) Mohaghenghpour *et al* was cited by the Examiner for the teaching of importance of CTL in protective immunity against M. *tuberculosis* because the reference teaches first that a mycobacterial protein was implicated in immune protection against mycobacterial infection, second that a peptide subsequence from that protein is immunogenic in that it can elicit CTLs *in vitro* from T cells of uninfected persons, said T cells being capable of lysing autologous monocytes infected with M. *tuberculosis,* and third that CTLs with specificity for the said peptide are present in the circulation of M. *tuberculosis*-sensitized individuals, including patients with active TB.

7. For the purpose of prior art rejections, the filing date of the instant claims 1-4, 24, 25, 30 and 32-44 is deemed to be the filing date of the 60/264,987 provisional application, i.e. 1/30/01, as the 60/255,292 application does not support the claimed limitations of the instant application. The limitation recited in instant claims 1, 33 and 36 "wherein said" immunogen or molecule "is not hsp65 protein" and the limitation recited in instant claims 3, 35 and 38 "at least 5 copies of one or more" are not disclosed in the 60/255,292 application.

The Examiner notes Applicant's argument on page 17 of Applicant's said amendment that Applicant is always free to insert any limitation disclosed in the application as filed for purposes of avoiding prior art, i.e., "is not hsp65 protein", and the dates of priority cases versus prior art references is of no relevance, but the Examiner does not find Applicant's argument persuasive. Although the limitation "wherein said" immunogen or molecule "is not hsp65 protein" is not new matter, the said limitation does not find support in the 60/255,292 application for the purpose of prior art rejections.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 39 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by SwissProt_42 Accession No P06806.

SwissProt_42 Accession No P06806 teaches a protein from M. *bovis* and M. *tuberculosis* that is a purified 65kDa antigen that can elicit a strong immune reaction in animals infected with M. tuberculosis, and that the said protein is one of the major immunoreactive proteins of mycobacteria. SwissProt_42 Accession No P06806 further teaches that the protein is a HSP from the HSP60 family. SwissProt_42 Accession No P06806 teaches that amino acid residues 415-423 are a subsequence of the said protein, which is identical to SEQ ID NO: 5 (TLLQAAPTL) of the instant claims.

10. Claims 24 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by PIR_78 Accession No D70888.

PIR_78 Accession No D70888 teaches hypothetical protein Rv3808c from M. *tuberculosis* and amino acid residues 4-12 or LAASLLSRV, a subsequence of the protein that is identical to SEQ ID NO: 1 of the instant claims.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 36-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over SwissProt_42 Accession No P06806 in view of Mohagheghpour et al (J. Immunol. 1998, 161: 2400-2406) and Ruppert et al (Cell 74: 929-937, 1993).

SwissProt_42 Accession No P06806 teaches a protein from M. *bovis* and M. *tuberculosis* that is a purified 65kDa antigen that can elicit a strong immune reaction in animals infected with M. tuberculosis, and that the said protein is one of the major immunoreactive proteins of mycobacteria. SwissProt_42 Accession No P06806 further teaches that the protein is a HSP from the HSP60 family. SwissProt_42 Accession No P06806 teaches that amino acid residues 415-423 are a subsequence of the said protein, which is identical to SEQ ID NO: 5 (TLLQAAPTL) of the instant claims.

SwissProt_42 Accession No P06806 does not teach the isolated peptide TLLQAAPTL, nor a composition comprising a pharmaceutical carrier and the said peptide.

Mohagheghpour et al teach importance of CTL in protective immunity against M. *tuberculosis,* and further teach screening of a major target antigen protein of M. *tuberculosis* for subsequences of between 8 and 10 amino acid residues that contain the HLA-A201 binding motif and immunogenicity of the said subsequence(s) in humans. Mohagheghpour et al teach the binding motif of HLA-A201 is taught by Ruppert et al (Cell 74: 929-937, 1993, see below). Mohagheghpour et al teach that their findings are relevant for both vaccine development and adoptive immunotherapy. Mohagheghpour et al teach the peptides suspended in a pharmaceutical carrier. In particular, Mohaghenghpour *et al* teach a peptide from the said target protein is immunogenic in that it can elicit CTLs *in vitro* from T cells of uninfected persons, said CTLs cells being capable of lysing autologous monocytes infected with M. *tuberculosis*. Mohagheghpour et al teach that CTLs with specificity for the said peptide are present in the circulation of M. *tuberculosis*-sensitized individuals, including in patients with active TB. Mohagheghpour et al teach the inclusion of more than one peptide in a pharmaceutical (see entire article, especially last paragraph, abstract, introduction).

Ruppert et al teach peptides of 9 or 10 amino acid residues in length containing the canonical anchors L or M in position 2 and V, L or I at the C-terminal position.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the HLA-A201 peptide binding motif taught by Mohagheghpour et al and by Ruppert et al to scan the sequence of the major 65kDa immunoreactive protein from M. *tuberculosis* taught by SwissProt_42 Accession No P06806 for subsequences possessing the binding motif and possessing the potential to be an immunogenic CTL epitope, i.e., to arrive at the sequence TLLQAAPTL, this procedure as taught by Mohagheghpour et al for another major target antigenic protein of M. *tuberculosis*, and to have suspended it in a pharmaceutically acceptable carrier as taught by Mohagheghpour et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a peptide that can bind to HLA-A201 and potentially be recognized by M. *tuberculosis* specific CTL since Mohagheghpour et al teach the importance of CTL in protective immunity against M. *tuberculosis* and that the finding of peptides that bind to HLA-A201 from M. *tuberculosis* antigenic proteins are relevant for vaccine development and for adoptive immunotherapy, and SwissProt_42 Accession No P06806 teaches that their 65 kDa HSP is one of the major immunoreactive proteins of mycobacteria. With regard to the limitation of "An immunogen comprising a peptide segment" recited in claim 1, the said peptide would be expected to be immunogenic for antibody production since it comprises the minimum of 6 amino acid residues known in the art to be the size of an antibody epitope.
With regard to the inclusion of claim 39 in this rejection, the peptide TLLQAAPTL is identical to SEQ ID NO: 5 of the instant claims and therefore it has a sequence differing by no more than one amino acid residue from SEQ ID NO: 5. With regard to the limitation recited in base claim 36, "that induces a CTL-response", it is an expected property of the art peptide that it would induce a CTL response because it binds to HLA-A2.1 on the surface of M. *tuberculosis* infected cells.

Applicant's arguments in Applicant's amendment filed 4/29/05 have been fully considered, but are not persuasive.

Applicant's position is of record in the said amendment on pages 17-19: briefly, that (1) Swissprot_42 reference does not hint that the sequence of SEQ ID NO: 5 is important in any way, and the other references do not teach it; (2) Ruppert et al is offered to suggest the use of peptides of certain length or having certain amino acid residues at specified positions, and SEQ ID NO: 1 does not meet the Ruppert criteria in that there is no L or M at residue 2, and Mohagheghpour et al makes no mention of Swissprot_42 as a likely candidate for finding immunologically useful peptides, and used dendritic cells that express class II MHC molecules, so no motivation exists to search for immunogens using the teaching of Mohagheghpour et al ; (3) the algorithm in SwissProt_42 can not predict the discovery of the instant invention, that the peptide is actually processed and presented by cells in which the parent molecule, the 65kDA antigen is expressed; (4) that the Examiner allegedly holds the position that it would have been obvious to look

for any kind of peptides from all manner of proteins in order to find useable epitopes, and this constitutes an "obviousness to try" type of rejection.

It is the Examiner's position that: (1) the references are being argued separately by Applicant and Swissprot_42 is relied upon for the teaching that the protein that SEQ ID NO: 5 derives from is one of the major immunoreactive proteins of mycobacteria; (2) Ruppert et al is relied upon for the teaching of peptides that bind to HLA-A2.1 are of 9-10 amino acid residues in length and contain certain canonical anchor residues at anchor positions and SEQ ID NO: 5 recited in the instant claims possesses the canonical anchor residues, whereas SEQ ID NO: 1 is not recited in the claims under rejection so it is a moot point that SEQ ID NO: 1 does not possess the Ruppert et al motif; (3) and (4) SwissProt_42 does not teach the algorithm referred to by Applicant, but rather Ruppert et al teach the said algorithm. It is not necessary that the references teach that the peptide is actually processed and expressed by the cells in which the parent protein is expressed because the claims are drawn to a composition of matter, not to a method of immunizing using the peptide. The teachings are that the protein is a major immunogenic protein of mycobacteria, that algorithms are used to predict peptide subsequences from an immunogenic protein of origin that can potentially bind to an MHC class I molecule and elicit a CTL response or to react with CTL. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made and with a reasonable expectation of success to have utilized the algorithm taught by Ruppert et al on the physiologically relevant major immunogenic target protein sequence 65kDa antigen taught by SwissProt_42 that elicits a strong immune response to mycobacterial species in *in vivo* infected animals to produce the peptide with the sequence of SEQ ID NO: 5 that conforms to the Ruppert et al motif because Mohagheghpour et al teach scanning another major target immunogenic protein of mycobacteria using the Ruppert et al motif to identify peptide subsequences that bind to HLA-A2.1 and are immunogenic. The Examiner does not hold the position that it would have been obvious to look for any kind of peptide from all manner of proteins in order to find useable epitopes. SwissProt_42 teaches that the protein is a major immunoreactive protein of mycobacteria and not just any protein or any kind of peptide as alleged by Applicant, said peptides being presented by MHC class I molecules. Irrespective of the fact that the antigen presenting cells taught by Mohagheghpour et al express both class I and Class II MHC molecules, the peptides were of length for MHC class I binding to HLA-A2.1, not for binding to MHC class II, and they possessed the Ruppert et al motif for binding to the said class I MHC molecule and elicited class I MHC restricted CTL. It is therefore the Examiner's position that Mohagheghpour et al provides the motivation to search for HLA-A2.1 binding peptide immunogenic subsequences in major immunogenic proteins of M. *tuberculosis* such as the one taught by Swissprot_42 using the Ruppert et al motif for identifying candidate peptides that bind to MHC class I molecule HLA-A2.1.

13. Claims 38 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over SwissProt_42 Accession No P06806 in view of Mohagheghpour et al (J. Immunol. 1998, 161: 2400-2406) and Ruppert et al (Cell 74: 929-937, 1993) as applied to claims 1, 2, 4, 14, 24, 25 and 30 above, and further in view of U.S. Patent No. 5,662,907A.

SwissProt_42 Accession No P06806, Mohagheghpour et al and Ruppert et al have been discussed supra, hereafter, "the combined references".

The combined references do not teach wherein the immunogen comprises at least 5 copies of the peptide, nor a molecule comprising a plurality of peptides comprising SEQ ID NO: 5.

U.S. Patent No. 5,662,907A discloses that immunogenic peptides can be introduced into a host, including human, as a homopolymer of active peptide units, especially when being used in a vaccine composition (especially column 12).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a peptide/composition thereof comprising a homopolymer as disclosed by U.S. Patent No. 5,662,907A, including at least 5 copies of the immunogenic peptide taught by the combined references.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a more effective immunogen as disclosed by U.S. Patent No. 5,662,907A and because one of ordinary skill in the art at the time the invention was made would have been aware that increasing the size of the peptide would increase the half-life in circulation as pertains to digestion by proteases *in vivo*. In addition, the motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Section MPEP 2144.07.

Applicant's arguments in Applicant's amendment filed 4/29/05 have been fully considered, but are not persuasive.

Applicant's position is of record in the said amendment on page 19.

The Examiner's arguments enunciated in the base rejection supra apply herein.

14. Claims 24, 25 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over PIR_78 Accession No D70888 in view of Campbell, Harlow and Lane, and pET System Manual.

PIR_78 Accession No D70888 teaches hypothetical protein, i.e., one deriving from nucleic acid sequence having an open reading frame, Rv3808c from M. *tuberculosis* and amino acid residues 4-12 or LAASLLSRV, a subsequence of the protein that is identical to SEQ ID NO: 1 of the instant claims.

PIR_78 Accession No D70888 does not teach a composition comprising the protein taught by PIR_78 Accession No D70888 in a pharmacologically acceptable carrier.

Campbell teaches that it is routine to clone a gene and make monoclonal antibodies to the protein sometimes without a clear objective for their application (especially page 29 at the last paragraph). Campbell et al further teach method of producing monoclonal antibodies, wherein the method comprises injecting the antigen, or protein in this case, into a mouse (especially page 3).

Harlow and Lane teach immunizing mice to make monoclonal antibodies involves injecting antigen in a pharmacologically acceptable carrier, which for mice is complete Freund's adjuvant.

pET System Manual teaches a system for cloning and expression of recombinant proteins.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have cloned the protein taught by PIR_78 Accession No D70888 using the pET System Manual teachings and to have mixed the protein with a pharmaceutically acceptable carrier such as Freund's adjuvant as taught by Harlow and Lane for making monoclonal antibodies as taught by Campbell.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make monoclonal antibodies to the mycobacterial protein taught by PIR_78 Accession No D70888 because Campbell et al teach that it is routine to clone the gene for a protein and to make monoclonal antibodies to the protein even without a clear objective for their application and methods of producing monoclonal antibodies starting with injection of protein antigen into mice, and Harlow and Lane teach Freund's adjuvant is a pharmacologically acceptable carrier for protein antigens for injection into mice when making monoclonal antibodies.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
July 1, 2005

Christina Chan

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600